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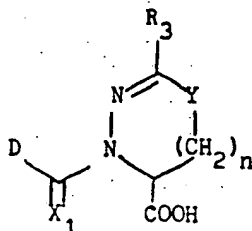
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5- and 6- Membered heterocyclic ring angiotensin converting enzyme inhibitors.

There are described compounds of formula I,

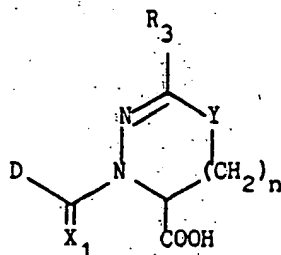


This invention relates to new compounds, methods for their preparation and compositions containing them.

A wide variety of angiotensin converting enzyme (ACE) inhibitors are known, eg from French Patent Specification No. 2,372,804 and European Patent Specification No. 0012401.

We have now found a group of compounds having advantageous properties, eg as ACE inhibitors.

According to the invention we provide compounds of formula I,



I

in which Y is S, O or NR₄,

n is 0 or 1,

R₄ is hydrogen or alkyl C 1 to 10,

R₃ is hydrogen, alkyl C 1 to 10, cycloalkyl C3 to 10, CF₃, SR₁₀, a 5 or 6 membered heterocyclic group containing one or more S, O or N atoms, NR₄R₅, phenyl or phenylalkyl C7 to 12, the phenyl, phenylalkyl and heterocyclic groups optionally being fused to a further phenyl group, the heterocyclic group and any phenyl group optionally being substituted by alkyl C 1 to 6, halogen, alkoxy C 1 to 6, nitro, nitrile, CF₃, SR₆, NR₄R₁₁, or hydroxy,

R₅, R₆ and R₁₁, which may be the same or different, are each hydrogen or alkyl C 1 to 10,

R₆ and R₁₁, which may be the same or different, are

each hydrogen, alkyl C 1 to 10 or phenyl,

R₁₀ is alkyl C 1 to 10,

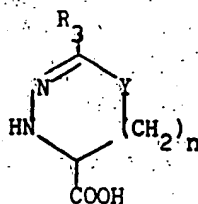
X₁ is S or O, and

D is a chain comprising from 2 -16 atoms, which chain carries an O or S containing substituent at a position 2 -6 atoms away from the group C=X₁,

and pharmaceutically acceptable salts, esters and amides thereof.

According to the invention we also provide a process for the production of a compound of formula I, or a pharmaceutically acceptable salt, ester or amide thereof, which comprises

- removal of a protecting group from a compound of formula I in which one or more of the amino or carboxylic acid groups is protected,
- reaction of a compound of formula II,

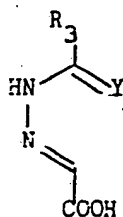


II

The starting materials for the above processes are either known or may be made from known compounds using conventional processes. Thus compounds of formula II in which n is 0 may be made by reaction of a compound of formula IV,



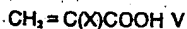
or a salt thereof,



or a salt, ester, amide or protected derivative thereof.

in which R_3 and Y are as defined above.

Compounds of formula II in which n is 1 may be made by reacting a compound of formula IV, or a salt thereof, with a compound of formula V,



or a salt, ester, amide or protected derivative thereof.

in which X is as defined above,

for example in a solvent which is inert under the reaction conditions, eg benzene, at a temperature of from 0° to 100°C and preferably of from 0° to 25°C and in the presence of a base, eg 1,5-diazabicyclo[4.3.0]non-5-ene.

Compounds of formula III may be made from the appropriate acid or a derivative thereof using conventional processes known per se.

The compounds of formula I, and the intermediates therefor, may be isolated from their reaction mixtures using conventional techniques known per se.

The processes described above may produce the compound of formula I or a derivative thereof. It is also within the scope of this invention to treat any derivative so produced to liberate the free compound of formula I, or to convert one derivative into another.

in which R_3 and Y are as defined above,

with glyoxylic acid (or a salt, ester, amide or protected derivative thereof)

eg in an alkanol such as ethanol, at room temperature.

The compounds of formula II may exist in the tautomeric form of formula VII,

VII

In addition to the processes described above the compounds of formula I may be made by a variety of processes which are analogous to those known for the production of structurally similar compounds.

We further provide the compounds of formula II and salts, esters, amides and protected derivatives thereof, which are useful as intermediates.

Pharmaceutically acceptable esters include esters with C1 to 10 alcohols, eg alkyl C 1 to 6 esters and esters with benzyl alcohol. The amides may be, for example, unsubstituted or mono- or di-C 1 to 6 alkyl amides and may be made by conventional techniques, eg reaction of an ester of the corresponding acid with ammonia or an appropriate amine.

We prefer compounds of formula I in which D is a chain comprising from 2 to 11 atoms, more preferably from 3 to 11 and most preferably from 3 to 6 atoms.

We prefer the atoms in chain D to be selected from C and N. We further prefer that less than 4 N atoms are present in the chain, more preferably less than 3 and most preferably only one. When there is one N atom in the chain we prefer it to be less than 5 atoms away from the group $C=X$, more preferably less than 3 atoms away and most preferably one atom away.

The chain may optionally be substituted. We prefer such substituents to be selected from alkyl C 1 to 10, phenyl and aminoalkyl C 1 to 6. We prefer the substituents to be at each or either end of the chain D. Thus when the substituent is alkyl C 1 to 10 or aminoalkyl C 1 to 6 we prefer it to be at the end adjacent the group $C=X$. The alkyl substituent is preferably alkyl C 1 to 6, more prefer-

Y is preferably O, or more preferably S.

We prefer n to be 0.

We prefer the -COOH substituent on the Y containing heterocyclic ring to be underivatised. We further prefer the asymmetric carbon atom of the Y containing heterocyclic ring to be in the S configuration.

R₁ is preferably hydrogen.

We particularly prefer the specific group of compounds of formula VIII in which Z is R₂CH-(COOH)NH-, Y is S, R is methyl or aminobutyl, n is 0, R₂ is n-propyl or phenylethyl and R₃ is t-butyl and pharmaceutically acceptable salts, esters and amides thereof.

The preferred salts of the compounds of formula VIII are maleates, hydrochlorides, ammonium salts or dicyclohexyl-ammonium salts.

The compounds of formula I may contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereo isomerism. Diastereoisomers may be separated using conventional techniques, eg chromatography or fractional crystallisation. The various optical isomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation. We prefer those compounds of formula I and formula VIII in which any asymmetric carbon atoms are in the S configuration.

The compounds of the invention are advantageous in that they are more efficacious, produce less side effects, are longer acting, more readily absorbed, less toxic, distributed in the body tissues in a different manner or have other advantageous properties when compared to compounds of similar structure.

The compounds of the invention are useful because they possess pharmacological properties. In particular they inhibit angiotensin converting enzyme and thus block conversion of the decapeptide angiotensin I to angiotensin II (see Example A). Angiotensin II is a potent vasoconstrictor in mammals. It also stimulates aldosterone release which results in salt and fluid retention. Increased blood pressure is the physiological result of these changes. Inhibitors of angiotensin converting enzyme are thus effective antihypertensive agents in a variety of animal models (see Example B) and are indicated for use clinically, for example, in patients with renovascular, malignant or essential hypertension or chronic congestive heart failure. See, for example, D W Cushman et al., *Biochemistry* 16, 5484 (1977) and E W Petrillo and M A Ondetti, *Med. Res. Rev.* 2 93 (1982).

Thus, the compounds of this invention are useful as antihypertensives in treating hypertensive mammals, including humans and they can be utilised to achieve reduction of blood pressure, eg in formulations containing appropriate pharmaceutically acceptable excipients, diluents or carriers. The compounds of the invention can be administered - (to animals or humans) in unit dosages of 1 to 500mg generally given several times, eg 1 to 4 times, per day thus giving a total daily dose of from 1 to 2000 mg per day. The dose will vary depending on the type and severity of disease, weight of patient and other factors which a person skilled in the art will recognise.

The compounds of this invention may be given in combination with other pharmaceutically active compounds, eg diuretics or antihypertensives. The dosage of the other pharmaceutically active compound can be that conventionally used when the compound is administered on its own, but is preferably somewhat lower. To illustrate these combinations, one of the antihypertensives of this invention effective clinically in the range, eg 1-200 milligrams per day, can be combined at levels ranging, eg from 1-200 milligrams per day with the following antihypertensives and diuretics in dose ranges per day as indicated:

hydrochlorothiazide (15-200mg), chlorothiazide (125-2000mg), ethacrynic acid (15-200mg), amiloride (5-20mg), furosemide (5-80mg), propranolol (20-480mg), timolol (5-50mg) nifedipine - (20-100mg), verapamil (120-480mg) and methyl-dopa (65-2000mg). In addition, the triple drug combinations of hydrochlorothiazide (15-200mg) plus amiloride (5-20mg) plus converting enzyme inhibitor of this invention (1-200mg) or hydrochlorothiazide (15-200mg) plus timolol (5-50mg), plus the converting enzyme inhibitor of this invention (1-200mg) are contemplated. The above dose ranges may be adjusted on a unit basis as necessary to permit divided daily dosage. Also, the dose may vary depending on the severity of the disease, weight of patient and other factors which a person skilled in the art will recognise.

According to our invention we also provide a pharmaceutical composition comprising preferably less than 80%, more preferably less than 50%, eg 1 to 20%, by weight of a compound of formula I, or a pharmaceutically acceptable salt or ester thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Thus the compound may be put up as a tablet, capsule, dragee, suppository, suspension, solution, injection, implant, a topical, eg transdermal, preparation such as a gel, cream, ointment, aerosol or a polymer system, or an inhalation form, eg an aerosol or a powder formulation.

A fast atom bombardment mass spectrum showed M^+560 (base peak 91).

$C_{21}H_{22}N_2O_5S$ requires MWt 559.

c) Benzyl 3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylate

A solution of the product from step b) (0.16g), pyrrolidine (0.16ml) and 3A molecular sieves (0.2g) in acetonitrile (3.2ml) was stirred at room temperature for 3.5 hours. The mixture was poured into water and extracted with ether, dried over magnesium sulphate and evaporated. The residue was flash chromatographed to give the sub-title product (0.05g) as a gum.

A fast atom bombardment mass spectrum showed M^+560 (base peak 91).

$C_{21}H_{22}N_2O_5S$ requires MWt 559.

d) 3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylic acid

A solution of the product from step c) (0.26g) in ethanol (20ml) was treated with 10% palladium on charcoal (0.1g) and stirred in a pressure vessel under hydrogen at 3 atmospheres at room temperature for 3 days. The catalyst was filtered off and the filtrate evaporated. The residue was triturated with ether to give the title product (0.08g) as a white solid, m.p. $180.5^\circ-182^\circ$.

A mass spectrum (FAB) showed M^+470 (base peak 234).

$C_{20}H_{20}N_2O_5S$ requires MWt 469.

Example 2

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(R)-carboxylic acid

A solution of the product from Example 1, step b) (0.43g) in ethanol (100ml) was treated with 10% palladium on charcoal (0.1g) and stirred in a pressure vessel under hydrogen at 3 atmospheres at room temperature for 3 days. The catalyst was filtered off and the filtrate evaporated. The residue was triturated with a mixture of ether and petroleum ether (bp $40^\circ-60^\circ$) to give the title product (0.19g) as a pale grey, non-crystalline solid.

A mass spectrum (FAB) showed M^+470 (base peak 234).

$C_{20}H_{20}N_2O_5S$ requires MWt 469.

Example 3

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-thiadiazole-2-carboxylic acid

a) Ethyl 2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-carboxylate

A solution of benzenecarbothioic acid hydrazide (0.4g) and ethyl glyoxylate (0.4g) in ethanol (1ml) was stirred at room temperature for 2 hours. The solvent was removed by evaporation and the residue re-evaporated with toluene (x2) to yield the sub-title product (0.7g) as a gum.

A mass spectrum showed M^+236 (base peak 163).

$C_{11}H_{12}N_2O_3S$ requires MWt 236.

b) Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-carboxylate

A solution of the product of step a) (2.36g) in toluene (100ml) was treated with polyvinylpyridine (2.0g) and 3-acetylthiopropionyl chloride (1.7g) and the mixture stirred at room temperature for 4 hours. The mixture was filtered and the filtrate stirred with a saturated solution of sodium bicarbonate (100ml) for 1 hour. The organic phase was separated, washed with water, dried and evaporated to a gum. The residue was purified by flash chromatography to give the sub-title product (2.62g) as an oil.

A mass spectrum showed M^+368 (base peak 163).

$C_{20}H_{20}N_2O_5S_2$ requires MWt 366.

c) 2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-thiadiazole-2-carboxylic acid

A solution of the product of step b) (2.6g) in methanol (20ml) was cooled to 0° under nitrogen and treated dropwise with a solution of potassium hydroxide (1.42g) in water (8ml). The mixture was allowed to warm to room temperature over 2 hours and then partitioned between ethyl acetate and water. The aqueous phase was acidified with 2N HCl and the organic phase separated, washed with water and dried. Evaporation yielded an oil which slowly crystallised to give the title product (0.7g) as white crystals, mp $145-6^\circ$.

A solution of the product from step a) (13.8g) and pyridine (6.6ml) in dichloromethane (136ml) was added over 0.5 hours under nitrogen to a stirred solution of trifluoromethanesulphonic anhydride (12.9ml) in dichloromethane (136ml) cooled to 5°C. After a further 0.5 hours the solution was washed with water, dried over magnesium sulphate, filtered and the filtrate evaporated.

The residue was taken up in dichloromethane (136ml) and added to a solution of N⁶-benzyloxycarbonyl-L-lysine t-butyl ester (15.5g) and triethylamine (6.5ml) in dichloromethane (136ml). The mixture was stirred at room temperature for 1 hour, heated under reflux for 2.5 hours, cooled, washed with water, dried over magnesium sulphate and filtered. The filtrate was evaporated and the residue purified by flash chromatography (ether/petroleum ether eluent) to separate and isolate the more polar SS isomer.

A solution of the SS t-butyl ester (0.5g) in ether (15ml) was cooled to +5° and saturated with hydrogen chloride for 2 hours. The solution was stirred at room temperature for a further 18 hours and the solvent was then removed by evaporation. Trituration of the residue in ether gave the sub-title product as a white solid (0.39g).

A fast atom bombardment mass spectrum showed M⁺533 (base peak 91).

C₂₁H₂₈N₄O₈ requires MWt 532.

c) Benzyl 3-[N⁶-benzyloxycarbonyl-N¹-(1-S)-benzyloxycarbonyl-3-phenylpropyl)-L-lysyl]-5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate

A stirred solution of the SS product from step b) (5.88g) and 1-hydroxybenzotriazole (1.35g) in dichloromethane (85ml) was treated with a solution of the product of Example 4, step a) (5.87g) in dichloromethane (80ml). A solution of dicyclohexylcarbodiimide (2.1g) in dichloromethane (85ml) was added over 5 minutes and the mixture was stirred at room temperature for 18 hours under nitrogen. Triethylamine (1.4ml) was added and the suspended solid removed by filtration. The filtrate was evaporated and the residue purified by flash chromatography to give the sub-title product as an oil (2.1g).

A fast atom bombardment mass spectrum showed M⁺793 (base peak 91).

C₄₆H₅₂N₈O₈S requires MWt 792.

d) Benzyl 3-[N⁶-benzyloxycarbonyl-N¹-(1-S)-benzyloxycarbonyl-3-phenylpropyl)-L-lysyl]-5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate

A solution of the product of step c) (2.1g) and pyrrolidine (1.6ml) in dry acetonitrile (60ml) was treated with crushed 3A molecular sieves and the mixture stirred at room temperature for 24 hours under nitrogen. The volatile materials were removed by evaporation and the SSS isomer separated from the more polar SSR isomer by flash chromatography. The SSS sub-title product (0.47g) was isolated as a clear oil.

A fast atom bombardment mass spectrum showed M⁺793 (base peak 91).

C₄₆H₅₂N₈O₈S requires MWt 792.

e) 5-t-Butyl-3-[N²-(1-S)-carboxy-3-phenylpropyl)-L-lysyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

A solution of the product from step d) (1.1g) in ethanol (90ml) was treated with 10% palladium on carbon (0.9g) and the mixture stirred under 1 atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration and the filtrate evaporated. The residue was recrystallised from a mixture of tetrahydrofuran and ethanol to give the title product as a white solid (0.24g).

mp slowly decomposes at 180-190°

Found: C 55.86 H 6.97 N 11.24 S 6.56 H₂O 2.83

C₂₇H₃₄N₄O₆S. 0.77H₂O

Requires: C 56.11 H 7.23 N 11.39 S 6.51 H₂O 2.82

A fast atom bombardment mass spectrum showed M⁺479 (base peak 84).

C₂₇H₃₄N₄O₆S requires MWt 478.

Example 6

5-t-Butyl-3-[N-(1-S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

a) Ethyl 2-(((trifluoromethyl)sulphonyloxy)-pentanoate

Under nitrogen, a solution of pyridine (11.9g) in dry dichloromethane (500ml) was rapidly stirred at -22° while trifluoromethane sulphonyl anhydride (40.5g) was added dropwise. After the addition, the white slurry was stirred at -22° for 15 minutes and then a solution of ethyl 2-hydroxy pentanoate (16.8g) in dichloromethane was added over 2 minutes at this temperature. The temperature was then allowed to rise to room temperature and the mixture was stirred vigorously for 1 hour, after which time the white solid was filtered off, washed well with dichloromethane and the combined washings

with benzyl 5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (1.6g). Dicyclohexylcarbodiimide (0.6g) was then added and the resulting mixture was stirred for 18 hours, filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography on silica eluting with diethyl ether/petroleum ether (60 -80°), 1:1 to give the required diester as an oil (1.1g)

NMR CDCl_3 , δ : 0.9(3H,t), 1.2-1.7(19H,m), 3.3-(1H,t) 4.2(3H,m), 5.2(2H,q), 6.18(1H,s) 7.35(5H,s).

e) Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonyl-butyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate

Under nitrogen, pyrrolidine (1.5ml) was added to a solution of the 'S,S,R' ester (step d) (1.6g) and the resulting solution was stirred at room temperature for 24 hours. The 1:1 mixture of S,S,R and S,S,S esters so produced was separated by flash chromatography on silica eluting with ethyl acetate/petroleum ether 60 - 80°, 1:3 to give 0.65g of each isomer. The S,S,R isomer was recycled such that the total conversion was 81%. NMR CDCl_3 , δ : 0.9(3H,t), 1.2-1.7(19H,m), 3.3(1H,t) 4.2-(3H,m), 5.17(2H,s), 6.18(1H,s)

7.35(5H,s).

f) 5-t-Butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

The S,S,S benzyl ester from step e) (1.8g) in ethanol (500ml) was hydrogenated over 10% Pd on charcoal (1.8g) at atmospheric pressure and room temperature for 5 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was triturated with a 1:1 mixture of ether/petroleum ether 60 -80° to give the required acid as a white solid (1.3g). mp 183 -5°.

Found: C, 47.13; H, 7.89; N, 9.31; S, 7.12%

$\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_5\text{S}$. 2.5 H_2O requires

C, 47.22; H, 7.87; N, 9.72; S, 7.41%

Example 7

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-[4-(methylthio)phenyl]-1,3,4-thiadiazole-2-(S)-carboxylic acid

a) 1-[(4-(Methylthio)phenyl)thioxomethyl]pyrrolidine

A mixture of 4-(methylthio)benzaldehyde (50.0g) and sulphur (15.8g) was cooled to 0° and pyrrolidone (41.1ml) was added over 30 minutes. On complete addition the whole was heated under reflux for 1.5 hours. The mixture was poured, whilst warm, into ethanol (250ml) and the resulting solid filtered off. Recrystallization from ethanol afforded the sub-title compound as a fawn, crystalline solid, (71.3g). mp 116.5-118°.

b) 4-[4-(Methylthio)phenyl]-4-(pyrrolidinium-1-ylidene)-3-thiobutanoic acid bromide

A solution of the product of step a) (20.0g) and bromoacetic acid (12.9g) in benzene (100ml) was stirred at room temperature under nitrogen for 18 hours. The resulting precipitate was filtered off and washed with ether to yield the sub-title compound (28.6g) as a white solid. mp 157-158°.

c) [4-(Methylthio)phenyl]thioxomethyl]thio]acetic acid

Hydrogen sulphide was passed through a solution of the product of step b) (25.0g) in methanol (250ml) and cooled in an ice bath, for a period of 3 hours.

After standing at 0° for 18 hours the solvent was removed under reduced pressure and the residue was triturated with water. The solid was filtered off and recrystallised from petroleum ether to afford the sub-title compound (16.7g) as a red crystalline solid. mp 117°.

d) 4-(Methylthio)phenylcarbothioic acid hydrazide

To a solution of the product of step c) (15.0g) in methanol (200ml) was added aqueous potassium hydroxide (58.0ml, 1M) followed by hydrazine monohydrate (3.1ml) dropwise over 30 minutes. After stirring at room temperature for 1 hour the mixture was acidified to pH.5 with concentrated hydrochloric acid. The resulting precipitate was filtered off and recrystallised from ethanol to afford the sub-title compound (9.9g) as pale yellow plates. mp 152-153°.

b) Benzyl 4-(3-acetylthio-1-oxopropyl)-2-cyclohexyl-5,6-dihydro-4H-1,3,4-thiadiazine-5-carboxylate

3-Acetylthiopropionyl chloride (0.45g) and poly-(4-vinylpyridine) (0.8g) were added to a solution of the product of step a) (0.86g) in dry toluene (20ml). The mixture was stirred under an atmosphere of nitrogen for 20 hours. Diethyl ether (30ml) was added and the mixture filtered. The filtrate was evaporated and the product purified by flash chromatography to yield the sub-title product (1.05g) as a pale yellow oil.

Mass spectrum (FAB) showed M^+449 (base peak 91).

$C_{25}H_{32}N_2O_4S_2$ requires MWt 448.

c) 2-Cyclohexyl-5,6-dihydro-4-(3-mercapto-1-oxopropyl)-4H-1,3,4-thiadiazine-5-carboxylic acid

1M Potassium hydroxide solution in methanol (5.83ml) was added to a solution of the product of step b) (0.87g) in methanol (10ml) and water (5ml). The mixture was stirred under an atmosphere of nitrogen for 2 hours. Acetic acid was added and the solvent evaporated under reduced pressure. The mixture was purified by flash chromatography using 1% acetic acid/ethyl acetate as eluent to yield the title compound (0.24g) as a white solid. mp 95-97°.

Mass spectrum showed M^+316 (base peak 156).

$C_{17}H_{20}N_2O_4S_2$ requires MWt 316.

Example 10

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-oxadiazole-2-carboxylic acid

a) Ethyl (benzoylhydrazono)acetate

A solution of benzoyl hydrazine (1.4g) and ethyl glyoxylate (1.32g) in ethanol (50ml) was stirred at room temperature for 24 hours. The solvent was evaporated and the residue treated with ether to give the sub-title product (1.8g) as white solid. mp 140-3°.

b) 3-(Acetylthio)propionic anhydride

A solution of 3-(acetylthio)propionic acid (3.4g) in ether (20ml) was treated dropwise with a solution of dicyclohexylcarbodiimide (2.1g) in ether with water-bath cooling. The mixture was stirred for 1.5 hours, filtered and the filtrate evaporated to give the sub-title product (3.2g) as a yellow oil.

c) Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-phenyl-1,3,4-oxadiazole-2-carboxylate

A mixture of the product from step a) (2.6g) and the crude product from step b) (3.2g) in pyridine (0.9ml) was heated at 100° for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The separated organic extract was washed with water, saturated aqueous sodium bicarbonate solution, water, dried and evaporated.

The residue was purified by flash chromatography to give the sub-title product (1.6g) as a yellow oil.

A mass spectrum showed M^+350 (base peak 147).

$C_{18}H_{18}N_2O_4S_2$ requires MWt 350.

d) 2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-oxadiazole-2-carboxylic acid

A solution of the product from step c) (1.44g) in methanol (40ml) was cooled to 15° under nitrogen and treated dropwise with a solution of potassium hydroxide (0.69g) in water (40ml). The mixture was stirred at room temperature for 2 hours and then the solvents were evaporated. The residue was taken up in water and washed with ether. The aqueous phase was acidified with 2N HCl and extracted with ethyl acetate. The separated organic phase was washed with water, dried and evaporated. The residue was purified by flash chromatography to give a pale yellow solid. The solid was taken up in dichloromethane, treated with charcoal, filtered and the filtrate evaporated to give the title product (0.24g) as an off-white solid. mp 106-9°.

Example 11

The following compounds were prepared from the appropriate starting materials by the processes described in Example 6.

Example 13

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylic acid

mp 67-9°

Found: C,48.37; H,7.99; N,9.42; S,7.2%

$C_{20}H_{30}N_4O_5S \cdot 2H_2O$ requires

C,48.22; H,7.80; N,9.93; S,7.57%

Example 14

5-t-Butyl-3-[N-(1-(R)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylic acid

mp 67-9°

Found: C,51.44; H,7.52; N,10.38; S,7.79%

$C_{20}H_{30}N_4O_5S \cdot 0.5H_2O$ requires

C,51.52; H,7.58; N,10.61; S,8.08%

Example 15

5-t-Butyl-3-[N-(1-(R)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

mp 124-5°

Found: C,52.46; H,7.63; N,10.77; S,8.07%

$C_{20}H_{30}N_4O_5S$ requires

C,52.71; H,7.49; N,10.85; S,8.27%

The following compounds were prepared by the method of Example 5 (using appropriate starting materials)

Example 16

3-[N-(1-(S)-Carboxy-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylic acid

mp softens at 151°, decomposes at 165-170°

A fast atom bombardment mass spectrum showed M^+442 (base peak 91)

5

$C_{25}H_{28}N_4O_5S$ requires MWt 441

Example 17

10

5-t-Butyl-3-[N-(1-(S)-carboxy-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

15

mp softens at 161°, decomposes at 179-184°

A fast atom bombardment mass spectrum showed M^+442 (base peak 91)

20

$C_{26}H_{28}N_4O_5S$ requires MWt 421

Example 18

25

5-t-Butyl-3-[N-(1-(S)-carboxybutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

mp 156-9°

30

The following compounds were prepared by the method of Example 4 (using appropriate starting materials).

35

Example 19

5-Cyclohexyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid

40

mp 136-138°

Example 20

45

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-(pyridin-3-yl)-1,3,4-thiadiazole-2-(S)-carboxylic acid

50

mp 160-3° (softens at c. 140°).

Example 21

55

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-isopropyl-1,3,4-thiadiazole-2-(S)-carboxylic acid

NMR spectrum (CDCl₃) of the compound showed characteristic peaks at delta 7.50 (4H,q,aromatic CHs), delta 2.34 (3H,s,-SC(=O)CH₃) and delta 6.30 (1H,s, heterocyclic CH).

Example 32

Benzyl 3-(3-acetylthio-1-oxopropyl)-5-benzyl-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate

Prepared using appropriate starting materials by process of Example 3 steps a) and b). The product was isolated as an oil.

NMR spectrum (CDCl₃) showed a characteristic signal at delta 6.17 (1H,s,heterocyclic CH).

Example 33

Benzyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-(2-phenylethyl)-1,3,4-thiadiazole-2-carboxylate

Prepared by similar processes to those of Example 3 steps a) and b). The product was isolated as an oil.

NMR spectrum (CDCl₃) showed a characteristic signal at delta 6.10 (1H,s,heterocyclic CH).

Example 34

Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-(naphthalen-2-yl)-1,3,4-thiadiazole-2-carboxylate

a) Naphthalene-2-carbothioic acid hydrazide

The sub-title product was prepared from appropriate starting materials by the processes of Example 7, steps a), b), c) and d). mp 166-167°

b) Ethyl 2,3-dihydro-5-(naphthalen-2-yl)-1,3,4-thiadiazole-2-carboxylate

Prepared from the product of step a) and ethyl glyoxylate by the process of Example 3, step a). The crude product was used without further purification.

c) Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-(naphthalen-2-yl)-1,3,4-thiadiazole-2-carboxylate

Prepared from the crude product of step b) and 3-acetylthiopropionyl chloride by the process of Example 3, step b). mp 107-108°

Mass spectrum (FAB) showed M⁺417 (base peak 213).

C₂₈H₂₈N₂O₄S₂ requires MWt 416.

Example 35

5-(Adamant-1-yl)-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylic acid

a) Methyl 1-adamantanecarbothioate

A mixture of 1-adamantanecarboxylic acid chloride (9.0g) and 2,4-bis-methylthio-1,2,3,4-dithiaphosphetan-2,4-disulphide (12.9g) in dry benzene was heated under reflux for 5 hours. The solvent was evaporated and the residue purified by flash chromatography to give the sub-title product - (6.2g) as a yellow solid.

mp 64.5-66°

b) Adamantane-1-carbothioic acid hydrazide

A solution of the product of step a) (1g) in methanol (50ml) was treated with hydrazine hydrate (0.3g) and the mixture stirred at room temperature for 1 hour. The solvent was evaporated, the residue triturated with water, and the pH adjusted to 7 to give the sub-title product (0.8g) as a white solid.

mp 204-206°

c) Ethyl 5-(adamant-1-yl)-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate

The product of step b) was treated with ethyl glyoxylate by the process of Example 3, step a) to give the sub-title product (1.5g) as an oil.

d) Ethyl 5-(adamant-1-yl)-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylate

The crude product of step c) was treated with 3-acetylthiopropionyl chloride by the process of Example 3, step b) to give the sub-title product as an oil.

Mass spectrum (FAB) showed M⁺425 (base peak 221).

C₂₈H₂₈N₂O₄S₂ required MWt 424.

	<u>% w/w</u>	<u>Range % w/w</u>
Compound of formula I	5	1-20
Microcrystalline cellulose	50	10-80
Spray dried lactose	37.75	10-80
Magnesium stearate	1	0.25-2
Colloidal silicon dioxide	0.25	0.1-1
Cross linked sodium carboxy methyl cellulose	3	1-5
Hydroxypropylmethylcellulose (coating)	3	1-5

25 Example D

This formulation is made up as a direct compression tablet, or without compression or coating, may be filled into a gelatine capsule.

30

	<u>% w/w</u>	<u>Range % w/w</u>
Compound of formula I	5	1-20
Microcrystalline cellulose	50	10-80
Lactose	35.75	10-80
Polyvinylpyrrolidone	2	1-5
Magnesium stearate	1	0.25-2
Colloidal silicon dioxide	0.25	0.1-1
Cross linked sodium carboxy methyl cellulose	3	1-5
Hydroxypropyl methyl cellulose (coating)	3	1-5

55

L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylate,

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(R)-carboxylic acid,

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-thiadiazole-2-carboxylic acid,

Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-carboxylate,

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate,

5-t-Butyl-3-[N¹-(1-(S)-carboxy-3-phenylpropyl)-L-lysyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 3-[N¹-benzyloxycarbonyl-N¹-(1-(S)-benzyloxycarbonyl-3-phenylpropyl)-L-lysyl]-5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 3-[N¹-benzyloxycarbonyl-N¹-(1-(S)-benzyloxycarbonyl-3-phenylpropyl)-L-lysyl]-5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate,

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate,

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-[4-(methylthio)phenyl]-1,3,4-thiadiazole-2-(S)-carboxylic acid,

t-Butyl 3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-[4-(methylthio)phenyl]-1,3,4-thiadiazole-2-(S)-carboxylate,

2,3-Dihydro-3-(3-mercapto-2-(S)-methyl-1-oxopropyl)-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 3-(3-acetylthio-2-(S)-methyl-1-oxopropyl)-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-carboxylate,

2-Cyclohexyl-5,6-dihydro-4-(3-mercapto-1-oxopropyl)-4H-1,3,4-thiadiazine-5-carboxylic acid,

Benzyl 4-(3-acetylthio-1-oxopropyl)-2-cyclohexyl-5,6-dihydro-4H-1,3,4-thiadiazine-5-carboxylate,

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-oxadiazole-2-carboxylic acid,

Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-phenyl-1,3,4-oxadiazole-2-carboxylate,

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-[4-(trifluoromethyl)phenyl]-1,3,4-thiadiazole-2-carboxylic acid,

Benzyl 3-[3-acetylthio-1-oxopropyl]-2,3-dihydro-5-[4-(trifluoromethyl)phenyl]-1,3,4-thiadiazole-2-carboxylate,

Benzyl 4-[3-acetylthio-1-oxopropyl]-5,6-dihydro-1-methyl-2-phenyl-4H-1,3,4-triazine-5-carboxylate,

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylic acid,

5-t-Butyl-3-[N-(1-(R)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylic acid,

5-t-Butyl-3-[N-(1-(R)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

3-[N-(1-(S)-Carboxy-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylic acid,

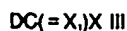
5-t-Butyl-3-[N-(1-(S)-carboxy-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

5-t-Butyl-3-[N-(1-(S)-carboxybutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

5-Cyclohexyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

or a salt, ester, amide, tautomer, or protected derivative thereof,

in which R_3 , Y and n are as defined in Claim 1 with a compound of formula III,

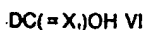


in which D and X_n are as defined in Claim 1, and X is a good leaving group,

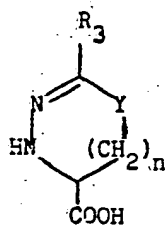
c) conversion of a compound of formula I, as defined in Claim 1, in which the asymmetric carbon atom of the Y containing heterocyclic ring is in the R configuration into a corresponding compound in which that carbon atom is in the S configuration,

d) reaction of a compound of formula II, in which R_3 , Y and n are as defined in Claim 1,

with a compound of formula VI,



in which D and X_n are as defined in Claim 1,



in which Y is S, O or NR_4 ,

n is 0 or 1,

R_4 is hydrogen or alkyl C 1 to 10,

R_3 is hydrogen, alkyl C 1 to 10, cycloalkyl C3 to 10, CF_3 , SR_4 , a 5 or 6 membered heterocyclic group containing one or more S, O or N atoms, NR_4R_4 , phenyl or phenylalkyl C7 to 12, the phenyl, phenylalkyl and heterocyclic groups optionally being fused to a further phenyl group, the heterocyclic group and any phenyl group optionally being substituted by alkyl C 1 to 6, halogen, alkoxy C 1 to 6, nitro, nitrile, CF_3 , SR_4 , NR_4R_4 , or hydroxy,

R_4 , R_3 and R_4 , which may be the same or different, are each hydrogen or alkyl C 1 to 10,

e) production of a pharmaceutically acceptable salt of a compound of formula I, as defined in Claim 1, by treating a compound of formula I as defined in Claim 1,

or another salt, an ester or an amide thereof,

with a compound containing an available

pharmaceutically acceptable ion and capable of converting the compound of formula I or the other salt, ester or amide thereof, to a pharmaceutically acceptable salt of the compound of formula I,

and where desired or necessary deprotecting the resulting compound, or converting a compound of formula I to a pharmaceutically acceptable salt, ester or amide thereof or vice versa.

9. A compound of formula II,

II

R_4 and R_4 , which may be the same or different, are each hydrogen, alkyl C 1 to 10 or phenyl,

R_4 is alkyl C 1 to 10,

and salts, esters, amides and tautomers thereof.

10. A compound according to Claim 1 for use as a pharmaceutical.

11. A pharmaceutical formulation comprising a compound according to Claim 1 in admixture with a pharmaceutically acceptable diluent, excipient or carrier.

Claims for Austria

1. A process for the production of a compound of formula I,

converting the compound of formula I or the other salt, ester or amide thereof, to a pharmaceutically acceptable salt of the compound of formula I,

and where desired or necessary deprotecting the resulting compound, or converting a compound of formula I to a pharmaceutically acceptable salt, ester or amide thereof or vice versa.

2. A process according to Claim 1, wherein X, is O, D is ZCHR₂,

R is hydrogen, alkyl C 1 to 10 or alkyl C 1 to 6 substituted by NH₂,

Z is R₁CH(COOH)NH- or R₁SCH₂-,

R₁ is hydrogen or R₁CO-,

R₂ is alkyl C 1 to 10 or phenyl, and

R₃ is alkyl C 1 to 10 or phenylalkyl C7 to 12.

3. A process according to Claim 2, wherein Z is R₁CH(COOH)NH- and R₂ is alkyl C 1 to 10 or cycloalkyl C3 to 10.

4. A process according to Claim 2 wherein

Z is R₁CH(COOH)NH-,

Y is S,

R is methyl or aminobutyl,

n is O,

R₁ is n-propyl or phenylethyl,

R₂ is t-butyl, and

all asymmetric carbon atoms are in the S configuration.

5. A process according to Claim 1, wherein the compound of formula I is,

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

5-t-Butyl-3-[N¹-(1-(S)-carboxy-3-phenylpropyl)-L-lysyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid, and

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

and pharmaceutically acceptable salts thereof.

6. A process according to Claim 1, wherein the compound of formula I is,

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(S)-carboxylate,

3-[N-(1-(S)-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-(R)-carboxylic acid,

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-phenyl-1,3,4-thiadiazole-2-carboxylic acid,

Ethyl 3-(3-acetylthio-1-oxopropyl)-2,3-dihydro-5-phenyl-1,3,4-thiadiazole-2-carboxylate,

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate,

5-t-Butyl-3-[N¹-(1-(S)-carboxy-3-phenylpropyl)-L-lysyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

Benzyl 3-[N¹-benzyloxycarbonyl-N¹-(1-(S)-benzyloxycarbonyl-3-phenylpropyl)-L-lysyl]-5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate,

Benzyl 3-[N¹-benzyloxycarbonyl-N¹-(1-(S)-benzyloxycarbonyl-3-phenylpropyl)-L-lysyl]-5-t-butyl-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylate,

5-t-Butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(S)-carboxylic acid,

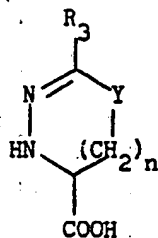
Benzyl 5-t-butyl-3-[N-(1-(S)-ethoxycarbonylbutyl)-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(R)-carboxylate,

dihydro-5-(naphthalen-2-yl)-1,3,4-thiadiazole-2-carboxylate,

5-(Adamant-1-yl)-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylic acid,

Ethyl 5-(adamant-1-yl)-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylate,

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-methyl-1,3,4-thiadiazole-2-carboxylic acid,



in which Y is S, O or NR₆,

n is 0 or 1,

R₆ is hydrogen or alkyl C 1 to 10,

R₃ is hydrogen, alkyl C 1 to 10, cycloalkyl C3 to 10, CF₃, SR₇, a 5 or 6 membered heterocyclic group containing one or more S, O or N atoms, NR₈R₉, phenyl or phenylalkyl C7 to 12, the phenyl, phenylalkyl and heterocyclic groups optionally being fused to a further phenyl group, the heterocyclic group and any phenyl group optionally

5-Cyclohexyl-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylic acid,

2,3-Dihydro-3-(3-mercapto-1-oxopropyl)-5-methylthio-1,3,4-thiadiazole-2-carboxylic acid, and

Benzyl 3-(N-(1-(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl)-2,3-dihydro-5-methylthio-1,3,4-thiadiazole-2-(S)-carboxylate,

and pharmaceutically acceptable salts thereof.

7. A compound of formula II,

II

being substituted by alkyl C 1 to 6, halogen, alkoxy C 1 to 6, nitro, nitrile, CF₃, SR₇, NR₈R₉, or hydroxy,

R₆, R₇ and R₁₁, which may be the same or different, are each hydrogen or alkyl C 1 to 10,

R₈ and R₉, which may be the same or different, are each hydrogen, alkyl C 1 to 10 or phenyl,

R₁₀ is alkyl C 1 to 10,

and salts, esters, amides and tautomers thereof.

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